Counterregulatory Hormones in Insulin-treated Diabetic Patients Admitted to an Accident and Emergency Department with Hypoglycaemia

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The aim of the study was (1) to describe hormone responses in insulin-induced hypoglycaemia and (2) to investigate if a combined treatment with intravenous glucose and intramuscular glucagon (group A) would improve glucose recovery as compared to treatment with intravenous glucose alone (group B). Eighteen adult patients with insulin-treated diabetes mellitus admitted to the Accident and Emergency Department with hypoglycaemia (plasma glucose 1.23 ± 0.15 mmol l^{-1} on admission) were randomized to one of the above treatments and plasma glucose and counterregulatory hormones were measured before and 30–120 min after treatment. Pre-treatment counterregulatory hormone concentrations were significantly lower than hormone concentrations during induced hypoglycaemia in healthy control subjects but significantly higher than healthy fasting concentrations for plasma adrenaline ($p = 0.020$), glucagon ($p = 0.008$), growth hormone ($p = 0.011$), and cortisol ($p < 0.00001$). Thus, although glucagon and adrenaline responses may be absent when studying Type 1 diabetic patients in the experimental setting, both hormones increase to a significant extent in 'real-life' hypoglycaemia in this patient group, although to a lesser degree than might be expected. Plasma glucose did not differ significantly between the two treatments at any time point. Despite access to food, one of four patients in group B and one of five patients in group A had plasma glucose below 4.0 mmol l^{-1} after 120 min. In conclusion, low yet significantly elevated concentrations of adrenaline and glucagon were found in diabetic patients admitted with severe hypoglycaemia to an Accident and Emergency Department.

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Introduction

Studies investigating counterregulatory hormone responses to hypoglycaemia have primarily been investigated in experimental laboratory conditions using insulin infusions or boluses, with or without other manipulations to test the role of individual hormones.[1] These studies have demonstrated major roles for glucagon and adrenaline in glucose counterregulation during acute hypoglycaemia, with more minor roles for cortisol and growth hormone.[1–3] In longer lasting hypoglycaemia, the rank order of the counterregulatory hormones is less clear but all of the above hormones seem to be important. Early studies showed important roles for cortisol and growth hormone;[4,5] later studies concluded that lack of glucagon or adrenaline would significantly reduce glucose recovery even in subacute hypoglycaemic state.[4–9] The secretion of glucagon in response to hypoglycaemia is abolished after only a few years of Type 1 (insulin dependent) diabetes mellitus and the secretion of adrenaline is reduced with longer diabetes duration.[10] To our knowledge these experimental results have never been examined in 'real life hypoglycaemia'. The present study therefore aimed at measuring counterregulatory hormones in IDDM patients admitted to the Accident and Emergency department with severe iatrogenic hypoglycaemia.

Recent studies underline the importance of recurrent hypoglycaemia in the development of hypoglycaemia unawareness.[11–14] It has been shown that patients are at risk of developing a second attack of hypoglycaemia shortly after the first attack of severe hypoglycaemia.[15–17] Prevention of an immediate second attack of hypoglycaemia may be attempted either by admitting the patients in the hospital for 24 hours or by administering food to the patients before they leave the emergency room. The frequency of recurrent hypoglycaemia after treatment of an index episode of hypoglycaemia has been reported to range between 2 and 30 %.[15–20] In the

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present study we have also compared two treatments of accidental insulin-induced hypoglycaemia: intravenous glucose alone and intravenous glucose supplemented by intramuscular glucagon;[21–23] with the hypothesis that a combined treatment might better achieve both a rapid and long lasting hyperglycaemic effect, with greater chance of avoiding a second attack of hypoglycaemia.

Patients and Methods

Patients

Eighteen patients with insulin-treated diabetes mellitus presenting to the Accident and Emergency Department at Hvidovre University Hospital with insulin-induced hypoglycaemia were enrolled. All 22 patients who attended with diabetes mellitus and hypoglycaemia on approximately 150 pre-selected days through a 1-year period (days and nights, weekdays, weekends, holidays) were included and randomized. Four were subsequently excluded: one patient did not wish to participate in the study, one patient had extremely high insulin levels, and deliberate over-dosage of insulin was suspected, one patient had Addison's disease, and one patient had Type 2 diabetes treated with oral agents. The clinical data for the included patients are presented in Table 1.

Informed consent was obtained from the patients after they recovered. Two patients were randomized twice (at intervals of 44 days and 57 days). One of them was randomized to a different treatment on each visit, therefore, the results from both visits were included for this patient. The other participated only with data from the first visit.

Data for baseline (euglycaemic) hormone concentrations and hormone concentrations during experimentally induced hypoglycaemia from a study of 11 healthy men (age 29.9 ± 2.6 years, weight 71 ± 2 kg, height 179 ± 6 cm) have been previously published[24] and were compared with our present study data.

The study was approved by the Local Ethics Committee for Copenhagen and Frederiksberg Kommune (J. nr V.200.2217/91), and was conducted within the regulations of the Helsinki II declaration.

Experimental Procedure

When patients with a diagnosis of iatrogenic hypoglycaemia attended the Accident and Emergency Department a clock was started and two intravenous cannulae were inserted. Thereafter, one of the following two treatments was administered in a randomized double-blinded way: intravenous glucose 25 g and placebo intramuscularly or intravenous glucose 25 g and glucagon (1.0 mg) intramuscularly. The powder consisting of pla-

Table 1. Individual anthopometric data and glucose data. Plasma concentrations (mmol l^{-1}) in insulin-treated diabetic patients before and after treatment with placebo and intravenous glucose (n = 11) or intramuscular glucagon and intravenous glucose (n = 9).

Treatment: intravenous glucose + intramuscular glucagon										
Patient ID	1[a]	2	3[a]	4	5	6	7	8	9	Mean ± SEM
Age/sex (M/F)	55/m	23/m	39/m	49/m	56/m	36/m	80/m	74/f	67/f	53 ± 6
Diabetes duration	30	7	1	1	34	23	64	61	13	24 ± 6
BMI		27			22	24		20	21	23 ± 1
Insulin dose (IU kg^{-1} BW)		0.7	0.5		0.6	0.3	0.5	0.3	0.3	0.47 ± 0.06
Haemoglobin A_{1c}		9.6	6.6	6.6	8.0	5.6			6.6	7.3 ± 0.6
Food intake	2	4	0	0	3		3	2	2	1.8 ± 0.6
t = 0 min	1.6	1.9	1.6	0.2	0.4	1.0	0.2	1.4	1.8	1.12 ± 0.23
t = 30 min	9.0	9.1	9.5	3.3	4.3	4.2	9.5	12.3	11.9	8.12 ± 1.12
t = 60 min	7.0	13.0	10.9	3.9	3.6	3.0	9.2	13.2	9.7	8.19 ± 1.78
t = 90 min		18.3	10.9		5.2	1.8	13.2	16.1		10.92 ± 2.6
t = 120 min		20.4			9.3	2.0	12.4	17.1		12.24 ± 3.19
Treatment: intravenous glucose + placebo										
Patient ID	10	11	12	13[a]	14	1	16	17	18[a]	Mean ± SEM
Age/sex (M/F)	32/m	29/m	31/m	30/f	51/m	42/m	56/m	46/m	40/m	39 ± 4
Diabetes duration	17	11	10	19	13	27	4	19	1	13 ± 2
BMI	26	23	20	28	18	23		23		23 ± 1
Insulin dose (IU kg^{-1} BW)	0.6	0.5	0.6	0.6	0.6	0.5		0.5	0.5	0.55 ± 0.01
Haemoglobin A_{1c}	7.4	7.6	13	6.1	8.2	6.2		8.5	7.5	8.1 ± 0.9
Food intake	3	4	2	0	0	6		4	0	2.8 ± 0.7
t = 0 min	2.1	2.2	1.4	1.5	1.1	1.1	0.5	1.1	1.1	1.33 ± 0.18
t = 30 min	2.9	8.1	6.8		5.0	3.9	1.0	9.9		5.37 ± 1.03
t = 60 min	2.8	6.3	6.1	7.7		8.6	4.5	14.7	5.7	7.06 ± 1.21
t = 90 min	4.4	4.3		7.6		12.3				7.15 ± 1.25
t = 120 min	6.9	3.4		7.9		15.2				8.35 ± 1.65

[a]Measurable serum ethanol.

cebo or glucagon was randomized, labelled and donated by Novo Nordisk A/S. The glucose (SAD, Copenhagen, Denmark) was administered as 50 ml of 50% glucose intravenously followed by flushing the line with 50 ml of isotonic saline. This is the standard initial treatment of severe hypoglycaemia in Danish Accident and Emergency Departments.

Intake of standardized food (sandwiches) and drink (juice) was encouraged on recovery and recorded in arbitrary units throughout the study period. One arbitrary unit was equal to one sandwich or 175 ml of juice. Blood samples for analysis of plasma glucose, glucagon, free insulin and catecholamines and serum cortisol and growth hormone were drawn just before administration of treatment (time = 0) and at 30-min intervals afterwards. Blood samples for serum ethanol were drawn at time 0. Eleven patients completed 120 min of follow-up. Nine patients could not be persuaded to stay in the Emergency Room for more than 30 min (1 patient), 60 min (7 patients) or 90 min (1 patient). The reason for leaving the experiment was that the patients felt completely normal. Analyses of glucose and of counterregulatory hormones were performed as previously described.[24]

During the experiment the reason for the attack of hypoglycaemia was discussed with the patient and this information was recorded. Information about previous medical history and haemoglobin A_{1c} was obtained from the patients' medical records if available (Department of Endocrinology, Hvidovre University Hospital, Hvidovre; Department of Endocrinology, Bispebjerg Hospital, Copenhagen and Steno Diabetes Center, Copenhagen).

An intravenous insulin tolerance test performed in 11 healthy controls lowered plasma glucose to 1.3 ± 0.1 $mmol^{-1}$ 25–30 min after the injection of 0.15 IU kg^{-1} BW of soluble insulin.

Results are described as mean (range) and mean ± SEM. Student's *t*-test for unpaired comparison was applied; for correlations Pearson's analysis was used; *p*-values less than 0.05 were considered significant.

Results

None of the patients offered any specific explanation for the hypoglycaemia episode. In four patients there was a measurable serum ethanol and one additional patient explained that he had been drinking heavily the day before.

Plasma glucose was 1.33 ± 0.18 mmol l^{-1} before treatment with intravenous glucose alone and 1.12 ± 0.23 mmol l^{-1} before treatment with intramuscular glucagon and intravenous glucose (Table 1). Hormone data are shown in Table 2. Plasma adrenaline was significantly and inversely correlated with plasma glucose ($p = 0.038$; for plasma glucagon the same correlation was not significant ($p = 0.106$). Neither serum cortisol ($p = 0.560$) nor serum growth hormone ($p = 0.156$) were significantly correlated with pre-treatment plasma glucose. Diabetes duration was significantly correlated neither with plasma glucagon ($p = 0.597$) nor with plasma adrenaline ($p = 0.655$). A multiple regression analysis with plasma adrenaline as dependent variable and plasma glucose and diabetes duration as independent variables showed borderline statistical significance for plasma glucose only ($p = 0.053$). For diabetes duration the test result was insignificant ($p = 0.763$). A similar test with plasma glucagon as dependent variable revealed no statistical differences, either for plasma glucose ($p = 0.210$) or for diabetes duration ($p = 0.620$).

As regards the mean differences between pre-treatment counterregulatory hormone concentrations of the 18 diabetic patients and hypoglycaemic concentrations during iatrogenic hypoglycaemia in 11 healthy controls (Table 3(a)), significantly higher concentrations were found for the healthy controls for adrenaline ($p<0.00001$), noradrenaline ($p = 0.039$), glucagon ($p = 0.00002$), and growth hormone ($p = 0.0003$). Cortisol concentrations were highest for the diabetic patients ($p = 0.007$). Plasma free insulin was higher for the healthy control subjects ($p<0.00001$). Mean differences between pre-treatment hormone concentrations in diabetic patients and fasting concentrations in healthy subjects (Table 3(b)) were significant for plasma free insulin ($p = 0.007$), plasma glucagon ($p = 0.008$), plasma adrenaline ($p = 0.020$), plasma cortisol ($p < 0.00001$), and plasma growth hormone ($p = 0.011$) but not for plasma noradrenaline ($p = 0.199$).

All patients regained consciousness within the first 30 min after treatment. As outlined in Table 1 plasma glucose did not differ significantly throughout the study. Recalculating the data without the patient who was included twice did not alter the statistical result. Among the nine patients completing 2 h observation time, one patient, who had received intravenous glucose only and one patient, who had received the combined treatment, had plasma glucose concentrations below 4.0 mmol l^{-1} at 120 min (Table 1).

Six patients had pre-treatment plasma free-insulin concentrations below 60 pmol l^{-1} (fasting values in normal subjects 30 pmol l^{-1}, range 16–57 pmol l^{-1}). The mean oral caloric intake was 2.8 (range: 0–6) arbitrary units in patients treated with intravenous glucose only and 2.0 (range: 0–4) arbitrary units in patients treated with glucose and glucagon ($p = 0.679$). One patient treated with intravenous glucose alone complained of nausea within the observation time. No side-effects to glucagon were observed within the observation time in these patients.

Discussion

The present study confirms in the clinical setting the inverse correlation between plasma adrenaline and plasma glucose during hypoglycaemia. This correlation has been demonstrated previously only during experimental hypoglycaemia and the observation supports results from previous studies concluding that adrenaline

Table 2. Pretreatment concentrations: Serum or plasma concentrations of counterregulatory hormones and free insulin in insulin-treated diabetic patients before treatment with placebo and intravenous glucose (n = 2) or intramuscular glucagon and intravenous glucose (n = 9). For comparison mean ± SEM for fasting concentrations and maximum concentrations during insulin-induced (0.15 IU kg^{-1} BW soluble insulin administered iv) from 11 healthy subjects are given

	Placebo + intravenous glucose (mean ± SEM)	Intramuscular glucagon + intravenous glucose (mean ± SEM)	Fasting values in 11 healthy subjects (mean ± SEM)	Max. values during induced hypoglycaemia in 11 healthy subjects (mean ± SEM)
Plasma glucagon (pmol l^{-1})	19.0 ± 4.8	15.6 ± 3.9	5 ± 1	57 ± 2
Plasma adrenaline (pmol l^{-1})	1279 ± 491	958 ± 296	154 ± 22	8296 ± 1146
Plasma noradrenaline (nmol l^{-1})	1.67 ± 0.49	1.66 ± 0.41	1.08 ± 0.12	2.90 ± 0.41
Serum cortisol (nmol l^{-1})	895 ± 76.46	873 ± 43.7	289 ± 36	706 ± 28
Serum growth hormone (μg l^{-1})	10.9 ± 4.1	11.3 ± 4.1	0.91 ± 0.14	31 ± 4
Plasma free insulin (pmol l^{-1})	122 ± 43	133 ± 31	30 ± 4	2435 ± 210

Table 3. Mean differences and p-values between hormone concentrations (a) after iatrogenic hypoglycaemia in healthy control subjects (n = 11) and in diabetic patients with insulin-induced hypoglycaemia (n = 18) and (b) during fasting in healthy control subjects (n = 11) and in diabetic patients with insulin-induced hypoglycaemia (n = 18)

	Mean difference and 95 % interval of confidence	p-values for mean difference
(a)		
Plasma glucagon (pmol l^{-1})	40 (24–55)	0.00002
Plasma adrenaline (pmol l^{-1})	7192 (5108–9276)	<0.00001
Plasma noradrenaline (nmol l^{-1})	1.20 (0.06–2.34)	0.039
Plasma growth hormone (μg l^{-1})	20.1 (10.3–29.9)	0.0003
Plasma cortisol (nmol l^{-1})	–178 (–52–(–304))	0.007
Plasma free insulin (pmol l^{-1})	2308 (1968–2648)	<0.00001
(b)		
Plasma glucagon (pmol l^{-1})	12 (3–21)	0.008
Plasma adrenaline (pmol l^{-1})	965 (167–1763)	0.020
Plasma noradrenaline (nmol l^{-1})	0.58 (–0.32–1.49)	0.199
Plasma growth hormone (μg l^{-1})	10.1 (2.54–17.8)	0.011
Plasma cortisol (nmol l^{-1})	595 (472–718)	<0.00001
Plasma free insulin (pmol l^{-1})	97 (29–165)	0.007

participates significantly in glucose recovery in long-term hypoglycaemia.[7,8]

Plasma concentrations of glucagon, adrenaline and noradrenaline, and serum growth hormone were significantly lower than the maximal concentrations for the same hormones during iatrogenic acute hypoglycaemia in healthy controls with a nadir of glucose slightly higher than that seen in the patients in the Accident and Emergency Department (Table 3(a)). This is in accordance with the suggestion that counterregulation is compromised in diabetic patients. On the other hand we demonstrated significantly higher concentrations for all of the above counterregulatory hormones in this patient group except for noradrenaline, when compared to fasting levels in healthy control subjects (Table 3(b)). This is an interesting finding, confirming in the clinical setting experimental results which showed increases in plasma glucagon and plasma adrenaline during hypoglycaemia induced with subcutaneous insulin[25] or with low doses of intravenous insulin.[26,27] Our results, therefore, challenge the statement[10,28] that glucagon and adrenaline counterregulation disappears with long standing diabetes. The reason for the difference may be a difference in plasma insulin as previously suggested.[26,27] Another explanation relates to the severity and the duration of hypoglycaemia in the present study, probably representing a greater stimulus to counterregulatory hormone secretion than seen in experimental settings.

On the other hand, despite the presence of glucagon and adrenaline, counterregulation (i.e. the spontaneous return of plasma glucose to normal levels) did not occur in our patients. Although all our control group were

male and some of our patients were female, the preponderance of males in our patient group makes gender an unlikely explanation for the magnitude of the difference.[29] This finding is in accordance with Caprio *et al*.[30] who demonstrated virtually abolished gluconeogenesis during long-term hypoglycaemia in diabetic patients despite a substantial increase in plasma adrenaline.

We observed levels of glucagon and adrenaline significantly above the fasting state, and we therefore suggest that not only reduced counterregulatory hormone levels but also impaired responsiveness of gluconeogenesis, perhaps due to ethanol in some patients, compromises counterregulation. Other factors could be increased hepatic sensitivity to insulin[31] or impaired responsiveness to adrenaline in the peripheral tissues. The latter mechanism contributes to glucose counterregulation during prolonged hypoglycaemia by decreasing peripheral glucose uptake.[32] Finally the effect of insulin as opposed to counterregulation has to be considered. This effect may be as important as an acute reduction in counterregulation. Surprisingly we found no correlation between plasma free insulin and plasma glucose. The pre-treatment insulin level in 6 patients was less than double our usual baseline (fasting) free insulin level. Two among these patients had a measurable serum ethanol. A plausible explanation for the low plasma free-insulin levels could be long standing hypoglycaemia with dissipation of the injected insulin; data on the possible duration of the hypoglycaemic episodes were however impossible to obtain.

The present study suggests in the clinical setting that a combined regimen for treatment of hypoglycaemia in insulin-treated diabetic patients consisting of both intramuscular glucagon and intravenous glucose does not increase plasma glucose levels more than treatment with intravenous glucose alone. However, we must emphasize that the present study group was small.

In the present study glucose concentrations in the latter part of the study period were not significantly higher after the combined treatment than after intravenous glucose alone. Looking at Table 1 with one exception with either treatment, if the blood glucose was in the normal range after 60 min then it did not fall again. On the other hand, two patients (one treated with the combined treatment, one treated with intravenous glucose only) among nine had plasma glucose concentrations below 4.0 mmol l^{-1} 2 h after treatment. This observation suggests that in the recovery phase of hypoglycaemia—despite encouragement to eat—these patients did in fact not eat enough to ensure a long lasting glucose recovery. Probably even mild, asymptomatic, recurrent hypoglycaemia may induce changes in thresholds for hormone secretion and awareness contributing to the development of hypoglycaemia unawareness.[33] It may, therefore, be suggested that patients recovering from iatrogenic hypoglycaemia should be offered more food. Whether this is achieved best by in hospital care or by self care is controversial.

In conclusion the present study demonstrates low but yet significantly increased plasma concentrations of adrenaline and glucagon in diabetic patients admitted with hypoglycaemia to an Accident and Emergency Department. The fact that blood glucose remained low despite significantly elevated counterregulatory hormone concentrations suggests that impaired responsiveness of gluconeogenesis contributes to counterregulatory failure.

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